REMARKS/ARGUMENTS

Claims 82, 84-96 and 98-121 are pending in the application. Claims 82, 84, 85-88, 90, 93, 96, 98, 100 and 102 have been withdrawn as a result of an earlier restriction requirement. Applicants retain the right to present these withdrawn claims in a divisional application. New claim 122 has been added. Claims 89, 91, 92, 94, 95, 99, 101 and 103-121 have been rejected. Reexamination and reconsideration of the claims are respectfully requested.

Applicants acknowledge with appreciation the withdrawal of the previous rejections of claims 109 and 115 under 35 U.S.C. §112 and the rejections of claims 89, 91-92, 94-95, 99, 101, and 103-120 for the recitation of certain terms and phrases.

New claim 122 has been added. Claim 84 was withdrawn as being drawn to a nonelected invention (Office Action of 11 October 2005, page 2, #2). Applicants note that claim 84 was drawn to the composition of claim 101 (*i.e.*, a composition comprising dendritic cells derived from a culture of a population of proliferating **dendritic cell precursors**) wherein the **dendritic cell precursors** are human. Thus, as discussed in the Preliminary Amendment filed 30 October 2003 (page 7, last paragraph), claim 84 was not directed to dendritic cell precursors but rather to a composition comprising dendritic cells derived from specified dendritic cell precursors. However, for the sake of clarity and to expedite prosecution, new claim 122 has been added to encompass this subject matter. Support for new claim 122 can be found in the specification, particularly, for example, on page 25, lines 10-12 and in working Example 6. No new matter has been added by way of amendment.

The Claims Meet the Requirements of 35 U.S.C. §112, First Paragraph

Claims 110, 118, and 119 stand rejected for failing to meet the written description requirement. Applicants respectfully traverse this rejection.

The Office Action concludes (page 3, #5) that the recitation in claim 110 of "wherein the cell aggregates are subcultured about every 3 to 30 days" is not adequately supported by original claim 14, which contained the additional phrase "one to five times." While Applicants believe that claim 14 does provide adequate support for claim 110 as previously presented, in order to expedite prosecution, claim 110 has been amended to include the additional phrase indicated in the Office Action. Accordingly, withdrawal of the rejection of claim 110 on this basis is respectfully requested.

PAGE 8/16 * RCVD AT 3/10/2006 11:49:28 AM [Eastern Standard Time] * SVR:USPTO-EFXRF-6/12 * DNIS:2738300 * CSID:19192876301 * DURATION (mm-ss):06-04

The Office Action concludes (page 3, #5) that the recitation in claim 118 of "1-48 hours" and in claim 119 of "about 20 hours" are not supported by the specification. However, these limitations are specifically disclosed in the specification on page 36, lines 9-24, which describe culturing dendritic cell precursors in the presence of antigenic particles for the indicated time periods. Accordingly, withdrawal of the rejection of claims 118 and 119 on this basis is respectfully requested.

Claims 89, 91-92, 94-95, 99, 101, and 103-121 are newly rejected under 35 U.S.C. § 112, first paragraph (Office Action of 11 October 2005, page 4, #9). The Office Action concludes that these claims fail to meet the written description requirement because the specification and claims as originally filed do not provide support for the invention as now claimed. The Office Action particularly points to claims 101 and 120 and states (page 5, "B," second paragraph) that "no support for the limitations of these claims as they are now recited has been submitted. Limitations have been added amendment by amendment such that the claimed invention has evolved into one that is not supported by the specification." Applicants respectfully disagree with this conclusion and traverse the rejection. However, in order to expedite prosecution, a discussion of the support provided in the specification is provided below.

As an initial matter, Applicants note the comment in the Office Action (page 5, last paragraph) that claim 101 changed between 7/09/01 and 4/12/02, "apparently without amendment." However, in a Preliminary Amendment filed together with a CPA on 3 January 2002, claim 101 was amended as follows:

> 101 (Twice amended). An *in vitro* composition comprising [an enriched and expanded] a population of [processed antigen presenting] antigen-activated dendritic cell precursors, wherein said antigen-activated dendritic cell precursors present processed antigen derived from an enriched and expanded population of proliferating [said] dendritic cell precursors, which were contacted *in vitro*, in the presence of GM-CSF, with antigen for sufficient time for said proliferating dendritic cell precursors to process and present said [processed] antigen.

This amendment is in the record in PAIR but is indexed as "Applicant Arguments/Remarks made in an Amendment" rather than as an amendment to the claims. However, the amendment was apparently entered, as it was referred to in the next Office Action dated 12 March 2002 (page 2, #2). This amendment should explain the changes in claim 101 noted in the Office Action.

PAGE 9/16 * RCVD AT 3/10/2006 11:49:28 AM [Eastern Standard Time] * SVR:USPTO-EFXRF-6/12 * DNIS:2738300 * CSID:19192876301 * DURATION (mm-ss):06-04

Applicants believe that the specification and original claims adequately support the claims in their present form. At present, claims 101 and 120 are as follows:

101. (Previously Presented) An *in vitro* composition comprising antigen-activated dendritic cells presenting fragmented antigen derived from an *in vitro* culture of an enriched and expanded population of proliferating dendritic cell precursors by a method comprising:

providing a tissue source comprising dendritic cell precursors;

optionally treating the tissue source comprising dendritic cell precursors to increase the proportion of dendritic cell precursors;

culturing the tissue source on a substrate in a culture medium comprising GM-CSF to obtain cell clusters;

subculturing the cell clusters to produce cell aggregates comprising proliferating dendritic cell precursors; and

subculturing the cell aggregates at least one time to enrich the proportion of dendritic cell precursors;

wherein the dendritic cell precursors are cultured *in vitro* in the presence of an antigen for a time sufficient to allow the antigen to be fragmented and presented.

120. (Previously Presented) An *in vitro* composition comprising antigen-activated dendritic cells, wherein said antigen-activated dendritic cells are derived from an *in vitro* culture of a population of enriched and expanded proliferating precursor cells which were contacted *in vitro* with antigen in the presence of GM-CSF for a sufficient time for antigen fragmentation and presentation to occur.

Support for the claim limitations in the specification includes the following. The first paragraph of the Detailed Description (page 19, lines 25-31) states that "[t]his invention relates to a method of producing **cultures of proliferating dendritic cell precursors** which mature ***in vitro*** to mature dendritic cells. The dendritic cells and the dendritic cell precursors produced according to the method of the invention may be produced in amounts suitable for various immunological interventions for the prevention and treatment of disease."

Antigen-activated dendritic cells are discussed, for example, on page 40, lines 25-28, which states that "[t]he present invention provides for the first time a method of obtaining dendritic cells in sufficient quantities to be used to treat or immunize animals or humans with dendritic cells which have been **activated with antigens**." Page 9, line 35 through page 10, line 3 states that "[a]nother embodiment of the invention [is] antigen-activated dendritic cells prepared according to the method of the invention in which antigen-activated dendritic cells have been exposed to antigen and express modified antigens for presentation to and activation of T

PAGE 10/16 * RCVD AT 3/10/2006 11:49:28 AM [Eastern Standard Time] * SVR:USPTO-EFXRF-6/12 * DNIS:2738300 * CSID:19192876301 * DURATION (mm-ss):06-04

cells." Page 42, lines 9-11, states that "**[a]ntigen-activated dendritic cells** and dendritic cell modified antigens may both be used to elicit an immune response against an antigen."

Antigen presentation is discussed, for example, on page 12, lines 26-29, which state that "[i]t is also an object of this invention to provide dendritic cell precursors capable of phagocytosing antigenic material to be processed and **presented** by the dendritic cell precursors." Antigen presentation is also discussed generally on page 5, line 27 through page 6, line 9. Support for "**fragmented antigen**" and "antigen fragmentation" can be found in the specification on page 5, lines 23-30; page 6, lines 4-32 and at page 36, lines 13-15. The Office Action dated 3 February 2004 (at part 10) acknowledged that the specification provides support for "an enriched and expanded population of dendritic cell precursors. "

Support for the method steps recited in the claims includes page 19, line 32 through page 20, line 2, which discusses that "[t]he starting material for the method of producing dendritic cell precursors and mature dendritic cells is a **tissue source** comprising dendritic cell precursors which precursor cells are capable of proliferating and maturing *in vitro* into dendritic cells when treated according to the method of the invention." Optional treatment of the tissue source to increase the proportion of dendritic cell precursors is discussed on page 20, line 33 through page 21, line 6, which states that "the tissue source may be treated prior to culturing to enrich the proportion of dendritic precursor cells relative to other cell types."

The culture of cells in culture medium supplemented with GM-CSF is discussed, for example, on page 24, lines 3-7. Additional support is provided on page 25, lines 19-26, which states that "**GM-CSF** has surprisingly been found to promote the **proliferation** in vitro of precursor dendritic cells. Cells are cultured in the presence of GM-CSF at a concentration sufficient to promote the survival and proliferation of dendritic cell precursors." Under these culture conditions, cell aggregates form which eventually give rise to dendritic cells (see, *e.g.*, page 26, lines 15-19. The culturing conditions and formation of cell aggregates are discussed, for example, on page 27, line 20 through page 30, line 3. Subculturing is discussed, for example, on page 28, lines 9-14 and page 29, line 20 through page 30, line 3.

Culturing cells in the presence of antigen is discussed, for example, on page 36, lines 30-32, which states that "[c]ells should be exposed to antigen for **sufficient time to allow antigens to be internalized and presented** on the cell surface." Presentation of antigens is further discussed, for example, on page 39, lines 16-18, which states that "[a]n important feature of the

PAGE 11/16 * RCVD AT 3/10/2006 11:49:28 AM [Eastern Standard Time] * SVR:USPTO-EFXRF-6/12 * DNIS:2738300 * CSID:19192876301 * DURATION (mm-ss):06-04

dendritic cells of this invention is the capacity to efficiently present microbial and other antigens on both class I and II products."

The Non-Statutory Double-Patenting Rejection

The Office Action (page 4, #7) has provisionally rejected claims 89, 91-92, 94-95, 99, 101 and 103-121 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 45 and 46 of the copending and later filed U.S. Patent Application No. 10/287,813.

The Examiner has acknowledged that Applicants have requested that this ground for rejection be held in abeyance until allowable subject matter is indicated.

The Rejection of Claims under 35 U.S.C. § 103(a) Should Be Withdrawn

The Office Action (page 6, #10) has rejected claims 89, 91-92, 94-95, 99, 101, and 103-121 under 35 U.S.C. § 103(a) over Sornasse *et al.* in view of Aldovini *et al.* Applicants respectfully disagree with this conclusion and traverse the rejection.

The Sornasse reference states that syngeneic dendritic cells pulsed *in vitro* with antigen induce a strong antibody response when injected into mice (page 15, Abstract). The dendritic cells studied by Sornasse were obtained from mouse spleens (page 15, column II). Sornasse actually discusses two populations of cells which are called 'dendritic cells' ("DC") and "low-density B cells," and which differ in their behavior as follows (page 16, column II, first paragraph):

> The two types of APC, however, have distinct properties. Indeed, 24-h-old, purified DC cultured with antigen only slightly induce the activation of the T cell hybridoma, whereas 24-h-old low-density B cells very efficiently present the antigen in the same conditions"

Sornasse's dendritic cells appear to be a population of nonadherent cells isolated after culture overnight in FCS-containing medium. While the procedure is not completely clear from the description in the Materials and Methods section, apparently the dendritic cells of Sornasse are then pulsed overnight with antigen (page 16, column I, second paragraph). However, as indicated above, these 'dendritic cells' "only slightly induce" the activation of a T cell hybridoma *in vitro*.

PAGE 12/16 * RCVD AT 3/10/2006 11:49:28 AM [Eastern Standard Time] * SVR:USPTO-EFXRF-6/12 * DNIS:2738300 * CSID:19192876301 * DURATION (mm-ss):06-04

In contrast to the 'dendritic cells' of Sornasse, dendritic cells prepared according to a method of the invention are very efficient at presenting antigen to T cells *in vitro*. The specification emphasizes the importance to the present invention that dendritic cells of the invention are capable of stimulating a T-cell response (see, for example, page 11, line 32 through page 12, line 1; page 34, lines 15-19; page 41, lines 29-34). Further, working Example 6 (pages 74-78) demonstrates that dendritic cells of the invention prepared from human blood produced a dramatic T cell response *in vitro* (see page 77, lines 5-15 and Figures 18A, B, and C). While these experiments are not identical to those performed by Sornasse, they illustrate that the dendritic cells taught by Sornasse have different properties from those of the present invention. Thus, the dendritic cells of Sornasse are not the dendritic cells of the present claims.

Sornasse also reports 'low density B cells' that "very efficiently present myoglobin to T cell hybridoma *in vitro*. Nevertheless, they only induce a weak primary B cell response *in vivo* as compared with DC" (page 18, column I). Sornasse notes that the observed behavior of the 'low-density B cells' may be due to contaminating DC (page 18, column I).

Regardless of whether either of the cell populations taught by Sornasse are actually DCs, the cells of the present invention have different and superior properties to those of Sornasse. Particularly, the cells of the present invention are cultured in GM-CSF, whereas those taught by Sornasse are not (see Sornasse at page 15, column II, "Culture Medium."). Independent claims 101 and 120 both require that cells are cultured with GM-CSF. The specification (page 25, lines 19-26) teaches that "GM-CSF has surprisingly been found to promote the proliferation *in vitro* of precursor dendritic cells. Cells are cultured in the presence of GM-CSF at a concentration sufficient to promote the survival and proliferation of dendritic cell precursors." Moreover, "[i]n the absence of GM-CSF, no colonies develop" (see page 26, line 19). Without forming colonies, the cells would be unable to form the "population of enriched and expanded proliferating precursor cells" of the present claims. Thus, the process used to make Applicants' claimed cells is different from the process described by Sornasse, and the cells that result from the different processes are also different. Thus, Sornasse does not teach the cells of the present invention.

Aldovini merely teaches the BCG antigen and does nothing to supplement the shortcomings of Sornasse. Accordingly, Applicants respectfully request that the rejection of claims as obvious over Sornasse in view of Aldovini be withdrawn.

PAGE 13/16 * RCVD AT 3/10/2006 11:49:28 AM [Eastern Standard Time] * SVR:USPTO-EFXRF-6/12 * DNIS:2738300 * CSID:19192876301 * DURATION (mm-ss):06-04

Applicants note that a rejection of claims was previously made over a combination of references that included a similar reference (the Inaba reference; see Office Action of 2 July 2002). Particularly, the Office Action of 2 July 2002 (page 6, #14) stated that:

> Inaba et al. teaches dendritic cells pulsed with polypeptide or peptide antigens...that process and present antigen.... The reference further teaches that said pulsed dendritic cells could be useful in 'a new approach to immunization' because of their natural adjuvant properties...."

The Inaba reference taught dendritic cells which were prepared without the benefit of culture in GM-CSF. The Inaba reference was discussed in several subsequent papers, and Applicants ultimately distinguished the Inaba reference in the Amendment filed 2 June 2004 (page 7, part I) by noting that :

> The so-called 'dendritic cells' of Inaba cannot be pulsed with native protein antigen after a *single day* in culture .... Inaba later states that his 'dendritic cells' can 'only capture antigens for a short period.' (page 198, paragraph spanning pp. 198-199). Thus, the so-called 'dendritic cells' of Inaba can uptake native protein antigens for only a short time, and lose this ability after a mere day in culture.
>
> In contrast, the Application describes the uptake of native protein antigen by dendritic cells *several days* after the cells are cultured. For example, in Fig. 13, the Application provides results showing that dendritic cells which were cultured for 6 days in GM-CSF, then exposed for 2 hours to GCG antigen, and then cultured another 2 days in GM-CSF were still able to express antigen from the native BCG antigen that they had been pulsed with. In other words, before the cells' initial exposure to BCG antigen, the cells had been cultured for *six days*, and were still able to uptake, process, and present BCG antigen.
>
> Thus, the cells of Inaba are not the result of the same process as Applicants' claimed cells, nor are the cells of Inaba the same cells as Applicants' cells.
>
> Moreover, because the cells of Inaba are not able to be cultured for more than a single day, the ordinarily skilled artisan would realize that Inaba's so-called 'dendritic cells' cannot be enriched and expanded, as is required by the presently claimed composition. Culturing the cells of Inaba for longer than one day will cause them to lose their ability to uptake native protein antigen. Thus, the ordinarily skilled artisan would realize that if an attempt is made to enrich and expand the cells of Inaba, the cells of Inaba

PAGE 14/16 * RCVD AT 3/10/2006 11:49:28 AM [Eastern Standard Time] * SVR:USPTO-EFXRF-6/12 * DNIS:2738300 * CSID:19192876301 * DURATION (mm-ss):06-04

> can no longer uptake antigen, and so cannot be antigen-activated, as is required by the present claims.
>
> Accordingly, the cells of Inaba are simply not the same as those of the claimed invention.

(emphasis in original)

Ultimately, the rejection over Inaba was withdrawn in the Office Action of 13 August 2004 (page 2, #2), which stated:

> In view of Applicant's remarks/arguments the previous rejections under 35 U.S.C. 103(a)...have been withdrawn. **In particular, Applicant's arguments that the cells of the instant invention are not the cells of the reference because the cells of the reference were not cultured in GM-CSF, has been found convincing.**

As noted above, culture in GM-CSF is essential to the development of *in vitro* cultures of proliferating precursor cells of the present claims. Neither the Inaba reference nor the Somasse reference nor any other cited reference taught this aspect of the invention. Accordingly, the claimed invention cannot be obvious and Applicants respectfully request that this rejection of the claims be withdrawn.

CONCLUSION

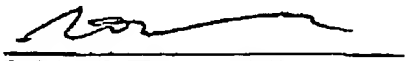
In view of the foregoing remarks, Applicants respectfully submit that all rejections have been overcome and that the claims are in condition for allowance. However, if the Examiner believes that any further discussion of this communication would be helpful, he is encouraged to contact the undersigned by telephone.

A Petition for an Extension of Time of two months and the required fee are submitted herewith. No additional fees or extensions of time are believed to be due in connection with this communication except for those indicated in documents accompanying this paper. However, if any additional extensions of time are necessary for the consideration of this paper, such

PAGE 15/16 * RCVD AT 3/10/2006 11:49:28 AM [Eastern Standard Time] * SVR:USPTO-EFXRF-6/12 * DNIS:2738300 * CSID:19192876301 * DURATION (mm-ss):06-04

extensions are petitioned under 37 CFR § 1.136(a). Please apply any charges that may be due for extensions of time or for net addition of claims to our Deposit Account No. 50-3187.

Respectfully submitted,



Leigh W. Thorne, Ph.D.
Attorney for Applicants
Registration No. 47,992

Date: 10 March 2006

Argos Therapeutics, Inc.
4233 Technology Drive
Durham, NC 27704
Tel: (919) 287-3419
Fax: (919) 287-6301

PAGE 16/16 * RCVD AT 3/10/2006 11:49:28 AM [Eastern Standard Time] * SVR:USPTO-EFXRF-6/12 * DNIS:2738300 * CSID:19192876301 * DURATION (mm-ss):06-04